Medical Progress

Intestinal Ischemia and Infarction Associated With Oral Contraceptives

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Thromboembolic vascular disease is a well-documented complication of oral contraceptive use. In all, 41 cases of mesenteric vascular ischemia or occlusion in women using oral birth control medications have been reported in the literature. "Reversible" ischemic enterocolitis or colitis (15 cases) and intestinal infarction (26 cases) represent the two clinical and pathologic presentations of this infrequently seen complication. Recovery is the rule in transient ischemia; clinically unmistakable intestinal necrosis carries a 31% mortality rate. Several pathophysiologic mechanisms, all unproved, have been proposed to explain these phenomena and the "hypercoagulable state." Recurrence is rare after the oral contraceptive regimen is discontinued.

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Oral contraceptives became available for use in the early 1960s. Since then, they have been prescribed for birth control, treatment of dysmenorrhea, menorrhagia, metromenorrhagia, endometriosis and suppression of postpartum lactation.[1] Their use peaked in the mid-1970s and has fallen slightly since, but it is estimated that more than 8 million American women and 50 million women worldwide are taking oral contraceptives.[1]

Not long after their introduction, however, adverse effects of oral contraceptives became known. The first report of a pulmonary embolus associated with the use of oral contraceptives was by Jordan in 1961[2] and was followed by several reports of superficial and deep vein thromboses, cerebrovascular accidents and myocardial infarctions in young women taking oral contraceptives. These alarming thromboembolic complications prompted several retrospective and prospective case-control and cohort studies that confirmed the increased risk of vascular events among oral contraceptive users. In a review of oral contraceptives and cardiovascular disease,[3] Stadel concluded that the relative risk among current users of oral contraceptives for idiopathic deep vein thrombosis or pulmonary embolus was 4 to 11 times, for myocardial infarction was 3 to 4 times and for stroke (thrombotic and hemorrhagic) was 5 times that of comparably aged women who never took birth control pills. Moreover, whereas smoking, increased age and estrogen content of the preparation appeared to increase these risks, the duration of oral contraceptive usage did not.

Although the numerous reports of complications of oral contraceptive use did not specifically address intra-abdominal vascular complications associated with them and therefore did not detail a definable risk of their occurrence, reports of more than 40 patients with small or large bowel (or both) ischemia or infarction have been published. The first such report in 1963 by Reed and Coon[4] was of the case of a 37-year-old woman, using oral contraceptives for two months, who had acute abdominal pain and at laparotomy was found to have gangrenous small bowel together with superior mesenteric vein occlusion with thrombus; she died postoperatively.

The exact incidence of thrombotic events of the abdominal vasculature has not been determined, as the information available has been presented as case reports from Europe and the United States and has not been subjected to vigorous cohort studies. Overall, 41 cases of "reversible" ischemic colitis or enterocolitis or of clinically unmistakable infarction have been reported in association with oral contraceptive usage.[4-25] These two broad clinical and pathologic categories can be subdivided according to distribution along major vascular trunks (celiac, superior mesenteric, inferior mesenteric) and according to the site of thrombus in either the arterial or the venous system (Table 1).

"Reversible" Ischemic Colitis or Enterocolitis

Of the 41 patients whose cases were reviewed, 15 (37%) presented with "reversible" ischemic colitis or enterocolitis. The clinical presentation was in all instances abdominal pain,

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TABLE 1.—*Clinical Presentation and Distribution of Vascular Lesions (N = 41)*

Presentation	*Vascular Distribution or Site of Thrombus*	*Patients, Number*	*Deaths, Number*	*Repeat Laparotomy, Number*
"Reversible" enterocolitis (N = 15)	Superior mesenteric	10	0	...
	"Watershed zone"	2	0	...
	Inferior mesenteric	3	0	...
Bowel infarction (N = 26)	Celiac artery	2	1	1
	Superior mesenteric artery	6	2	2
	Superior mesenteric vein	17	6	6
	Inferior mesenteric artery	1	0	0
	Inferior mesenteric vein	...	...	...

ABBREVIATIONS USED IN TEXT

HDL = high-density lipoprotein
SMA = superior mesenteric artery
SMV = superior mesenteric vein

usually colicky in nature, lasting from hours to weeks and associated with bloody diarrhea or gross hematochezia in 13 of 15 patients (87%). Nausea and vomiting were less consistently reported (5/15 or 33%). Fever, although not always present on admission, was reported at some time during the initial hospital stay in only a third of patients (5/15). Changes in stool caliber, anorexia and weight loss were not noted in the reports.

Evaluation of these patients was predominantly noninvasive. Leukocyte counts, described in only ten patients, were elevated ($> 10{,}000$ per μl) in all, and this was the only laboratory study with consistently abnormal results. Serum amylase levels were normal when reported. Plain radiographs of the abdomen were normal in most patients in whom these were done, although occasional reports of nonspecific large or small bowel ileus or bowel wall thickening were mentioned. Overall, barium contrast radiography was the most helpful diagnostic tool. Either the barium enema or upper gastrointestinal series with small bowel follow-through examination was abnormal in all 15 patients. Findings consisted of narrowed, spastic areas of colon or terminal ileum on barium enema examinations (Figure 1). The lesions were generally continuous but segmental in nature—that is, no skip lesions characteristic of Crohn's disease were observed. The mucosa was irregular and often ulcerated or spiculated. Characteristic "thumbprinting" was seen in 75% (6/8) of abnormal barium enemas. This finding, although not specific for intestinal ischemia, is thought to represent submucosal edema or hemorrhage, both of which are common pathologic changes in this disorder (Figure 2).

The three patients with abnormal small bowel barium radiographs had wall thickening, stenosis and rigidity with proximal dilation. The ileum was involved in all patients. "Thumbprinting" of the mucosa was seen in only one of these patients; no superficial mucosal irregularities were described.

Sigmoidoscopic and colonoscopic visualization of the involved areas added little to the diagnostic evaluation of these patients with "reversible" ischemic colitis or enterocolitis. Mucosal changes of friability, erythema and ulceration and luminal narrowing and spasm were encountered in some patients. Biopsy findings, when reported, were either normal or showed only nonspecific inflammatory changes. One could speculate about the potential usefulness of endoscopic biopsies for (1) noting rectal involvement, which would likely exclude ischemia as an etiologic factor, (2) discovering crypt abscesses or granulomas that could be suggestive of inflammatory bowel disease, (3) collecting mucosal biopsy specimens or exudate for culture to exclude infectious causes (tuberculosis, lymphogranuloma venereum, *Campylobacter* or *Yersinia*) or (4) diagnosing neoplasia. It appears, however,

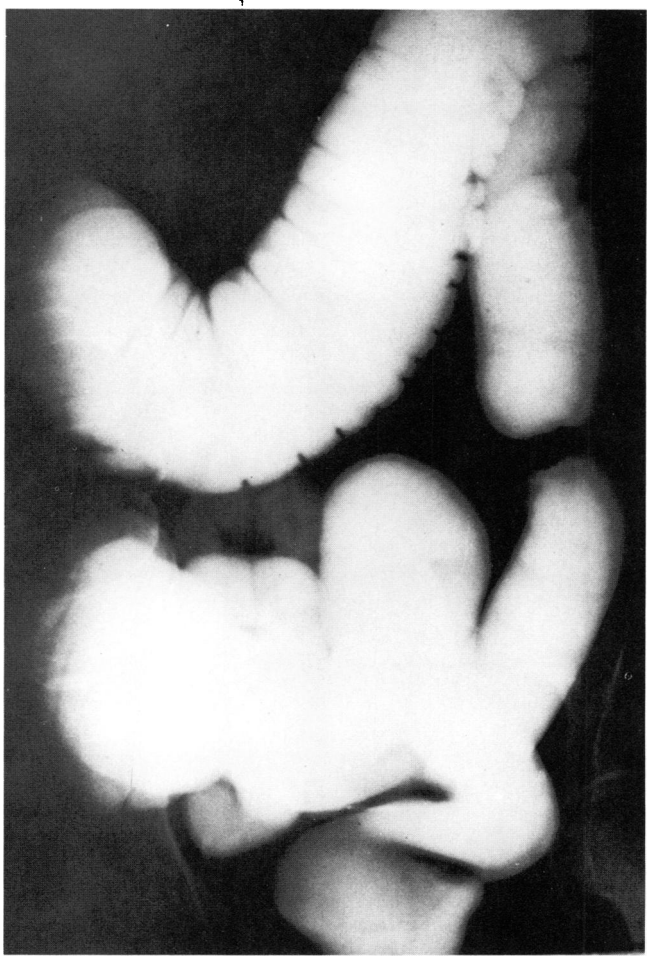

Figure 1.—Barium enema shows a focal stricture in the descending colon.

that these endoscopic studies did not obviate the need for barium examinations in these patients.

Three patients underwent laparotomy for diagnosis and treatment. We reported the case of a patient with a descending colon stricture from colitis that was resected for relief of pain and hematochezia and to confirm histologically the absence of carcinoma in the stricture, which could not be fully evaluated colonoscopically (Figure 3).[5] Of note, multiple thrombi in the branches of the inferior mesenteric artery were detected on microscopy. Similarly, Egger and Mangold described the case of a woman with a large bowel obstruction due to an inflammatory mass replacing the normal configuration of the distal transverse colon, splenic flexure and proximal descending colon.[6] A transverse colostomy was done without bowel resection. Gross pathologic examination of the vascular tree showed no abnormalities; the patient recovered and a follow-up barium enema three months later was normal. The third patient also was explored because of abdominal pain and hematochezia—at laparotomy an edematous ascending colon and normal mesenteric vessels were found.[7] No colotomy was done and she did well postoperatively.

The course of these 15 patients with reversible ischemic colitis or enterocolitis was one of gradual improvement while receiving supportive treatment within days to weeks after diagnosis and discontinuation of the oral contraceptive regimen. No patient was reported to have a recrudescence or reappearance of symptoms after the initial hospital admission and elimination of oral contraceptives. Indeed, these clinical observations were further corroborated in follow-up barium radiographs. Of the 11 patients with initially abnormal barium enemas as described above, 10 had repeat examinations from five to eight months later—9 were normal and 1 showed narrowing of the splenic flexure. The three previously abnormal small bowel barium radiograph examinations were all normal when repeated seven days to seven weeks later. None of these patients died of their illness.

The anatomic distribution of the abnormalities in ischemic colitis or enterocolitis can best be evaluated with respect to the large vessels serving the involved regions. Unfortunately, few pathologic specimens were provided in this less-seriously ill group. Two thirds of the patients had radiographic changes in the superior mesenteric artery distribution from the ligament of Treitz to the distal transverse colon, with a predominance of lesions in the terminal ileum and proximal half of the colon. Although the findings of neither arteriographic nor pathologic examinations are available that could confirm embolic disease, the predominance of abnormalities in this distribution and the wide luminal diameter and obliquity of the angle of the superior mesenteric artery at its origin from the aorta make this cause most likely.[26] Two patients had involvement in the "watershed zone" of the superior mesenteric and inferior mesenteric arterial distributions (distal transverse and proximal descending colon), and three patients had de-

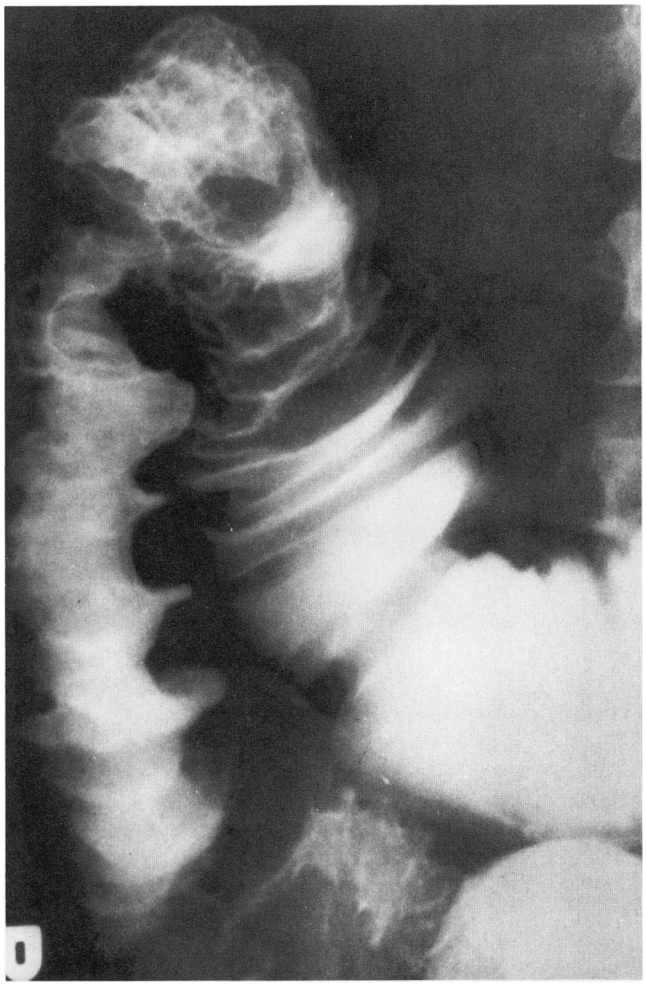

Figure 2.—Barium enema depicts "thumbprinting" of the ascending colon in ischemic colitis. The scalloped margins represent submucosal hemorrhage and edema, separated by haustral folds.

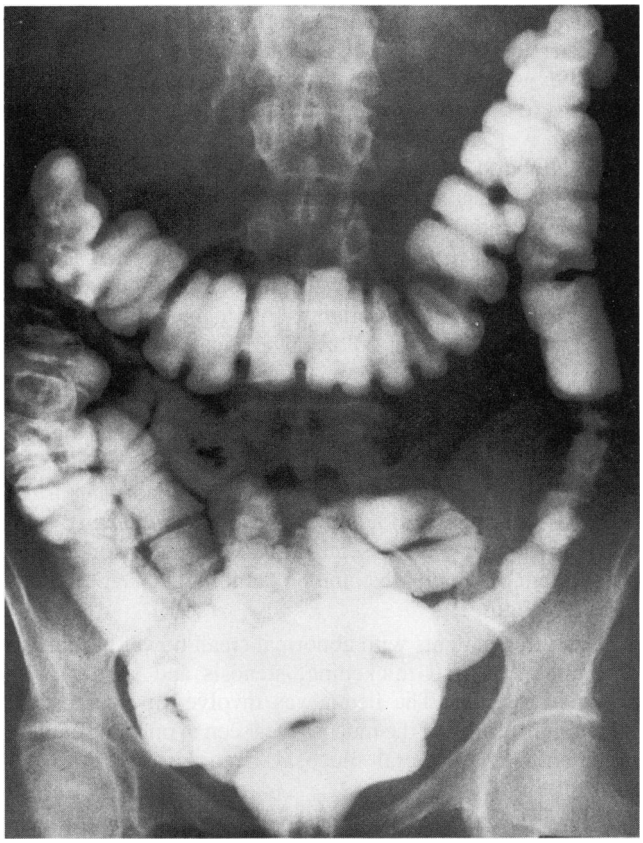

Figure 3.—Barium enema with persistent descending colon stricture and mucosal irregularity. Segmental resection of this region disclosed occluding arterial thrombi and focal colitis but no malignancy.

scending colon (inferior mesenteric) abnormalities. In one patient, arterial thrombi were discovered in a resected specimen.[5] As expected from the dual vascular supply of the rectum, no ischemia occurred here.

Bowel Infarction Among Users of Oral Contraceptives

There are case reports of 26 women using oral contraceptives who had documented bowel infarction. These women were obviously more seriously ill; in fact, 8 of 26 (31%) died of the vascular disease or postoperative complications. Vascular occlusion with thrombus of the branches of all three major distributions was documented, but disease location was skewed toward that of the superior mesenteric artery (SMA) and vein (SMV)—6 of 26 (23%) had disease in the SMA, 17 of 26 (65%) in the SMV. Two patients had vascular occlusion in celiac, superior mesenteric and inferior mesenteric arteries, one in both the SMV and inferior mesenteric vein, but the remainder showed only one trunk supply compromised.

As with reversible ischemia, abdominal pain was the presenting symptom in all of these patients. Crampy in nature, the pain had been present for up to 18 months before admission to hospital but, in general, symptoms prompting medical attention were of less than two weeks' duration in 24/25 (96%) for whom the information was provided; 19/25 (76%) had pain for less than one week and 7/25 (28%) had pain for less than 24 hours.

For patients with more prolonged pain, usually an exacerbation of the discomfort, the onset of vomiting (nine patients), diarrhea (three patients), hematochezia (two patients) or hematemesis (two patients) occasioned admission to hospital. Peritoneal signs, fever and hypotension were inconsistently reported. One patient with an abdominal bruit was noted.

As with reversible ischemia, leukocytosis and a normal serum amylase level were present in all but one patient for whom data were presented. Due to the acuteness of illness, radiographic evaluation was limited and, with the exception of free air on upright plain abdominal radiographs in two of four patients and barium enema evidence of splenic flexure and descending colon narrowing with "thumbprinting" in one of three done, was not helpful in diagnosis.

Of the 26 patients with bowel infarction, 25 underwent laparotomy for diagnosis, treatment or both. In all but three, resection was required of gangrenous, dusky, pale or edematous small or large intestine (or both) of varying lengths. Free peritoneal fluid or fecal contamination was infrequently reported. Thrombi occluding one or several lumina of arterial or venous structures were found in all patients, either grossly at laparotomy (eight patients) or following pathologic examination. A single patient showed necrotizing vasculitis of a branch of the inferior mesenteric artery without clot detected.[7] A 15-cm dark, indurated segment of descending colon was resected. A follow-up barium enema 17 days after the operation did not show any further evidence of ischemia.

The three patients in whom no resection was carried out are of special interest.[9,10] One patient with suspected intestinal infarction had multiple, nodular mesenteric venous occlusions but viable bowel. In a second patient, a thrombus occluding the SMA distal to the origin of the middle colic artery was removed and a previously pale section of small bowel regained normal color. The patient did well thereafter. A third woman undergoing laparotomy had edematous but viable small bowel with normal peristalsis. A thrill was felt at the celiac artery. No resection was done. Ten days later a recurrence of symptoms prompted reexploration, which disclosed gangrenous bowel from mid-small bowel to mid-ascending colon.

A second laparotomy was not uncommon. In fact, 11 of 26 (42%) required at least one additional exploration for further resection or repair of fecal fistulas. The findings of two "second-look" operations were unremarkable.

With two exceptions, both of whom had documented arterial occlusion of branches of all three major vascular trunks, recurrent ischemia or necrosis did not develop in any patient after oral contraceptive use was discontinued.[11]

In summary, therefore, two clinical presentations of ischemic bowel disease were noted among the overall group of 41 patients. All 41 women took birth control pills for varying durations—from 10 days to 10 years, with a mean of 2.2 years. The length of contraceptive use did not correlate with the severity of disease, presence of "reversibility" or mortality. These findings are consistent with data regarding other thromboembolic phenomena associated with oral contraceptive use.[3]

Pathogenesis of "Reversible" Ischemia

Can we incriminate the oral contraceptive drug as causative in these cases? Risk factors for intestinal ischemia such as polycythemia vera, the nephrotic syndrome, portal hypertension, atherosclerosis, surgical trauma and vasculitis were, with the exception of one case,[7] absent. "Spontaneous" ischemic colitis has been reported in young adults by Miller and co-workers[27] and Clark and associates.[28] Review of the combined data from these studies shows that 71% of the women in whom spontaneous ischemic colitis developed were using oral contraceptives at the time of diagnosis. Of note, one of the women not using the birth control pill was six months' pregnant, suggesting an endogenous elevation of estrogen and progestin levels as the cause of the ischemia.

It has been argued that the reversible colitis observed may not indeed represent ischemia.[29] The small number of cases necessitating resection and histopathologic confirmation of ischemia or thrombosis and the lack of angiographic evidence constitute the main objections. Indeed, the need for resection is unusual, with residual stricture and obstruction and uncertainty regarding the presence of neoplasm being the main indications. In this series, only one patient[5] required colonic resection for an ischemic stricture, and arterial thrombi were found in the specimen. Angiography, rarely used in this series, is a disappointing diagnostic tool,[30] as the main trunks are usually normal and the small marginal vessels, the most likely to be involved, are poorly seen. In older age groups, where atherosclerotic changes are to be expected, angiographic abnormalities are more frequently seen, but are less specific. The most useful evidence for an ischemic process appears to be the normalization of the barium enema changes of luminal narrowing, mucosal irregularities and thumbprinting,[31] occurring in 91% of patients.

Pathogenesis of Oral Contraceptive-Induced Intestinal Infarction

The issue is clearly much less controversial in the group of patients showing documented intestinal necrosis. Both venous

and arterial occlusions in major trunks and smaller vessels have been easily documented. The age of the patients involved and lack of preexisting risk factors make oral contraceptive use the likely cause.

The pathophysiology of oral contraceptive-induced ischemia and infarction is controversial and likely multifactorial (Table 2). In general, it is known that the highest incidence of thrombotic complications occurred when doses of estrogens and progestins were used far in excess of those needed for birth control.[32] When estrogen dosages in contraceptives were decreased by 50%, the reported incidence of venous complications fell from 25.9 to 7.2 per 100,000 users of oral contraception.[33] Arterial disease remained unchanged, but it appears that progestins are more implicated in arterial occlusion and estrogens in venous occlusion.[34,35]

In numerous articles, the effects of oral contraceptive agents on the clotting system have been evaluated. In general, the results are not uniform and in many cases are contradictory. Consistently, however, platelet count, prothrombin time and partial thromboplastin times are unchanged.

Platelet production of thromboxane A_2 has been reported to be increased,[36] and platelet aggregation seems less inhibited by endothelial cells[37] in oral contraceptives users. In a study in rabbits, no change was found in platelet aggregation in animals receiving both estrogens and progestins, which was attributed to an offsetting reduction in prostacyclin inhibition by the progestin component.[38]

Estrogens increase hepatic production of coagulation factors. Consistently, factor VII level and activity have been noted to be elevated in oral contraceptive users compared with those in controls.[38,40] Whether these elevations correlate with a "hypercoagulable state," however, is unclear since normally clotting factors circulating in the plasma are in greater concentrations than are needed for hemostasis.

Levels of antithrombin III, a protein that inhibits conversion of prothrombin to thrombin, have been reported to be normal or depressed in quantitative and functional analyses in oral contraceptive users. Differences in measuring techniques and individual variability have accounted for discrepant results. Still, when concentrations were depressed, they rarely reached the 40% to 55% levels considered to be associated with spontaneous coagulation.[41] Additionally, plasminogen activator levels were lower in some oral contraceptive users, correlating with depressed fibrinolysis and venous, but not arterial, thrombosis.[42] Thus, the clotting cascade and fibrinolytic system, especially elevated factor VII levels, depressed levels of antithrombin III and diminished fibrinolysis, *may* play supporting roles in the so-called hypercoagulable state.

The role of lipids and lipoproteins has also been noted.[34,39,43] Serum triglyceride levels are mildly but consistently elevated in oral contraceptives users, whereas total cholesterol levels are not. Levels of very-low-density lipoprotein and low-density lipoprotein, the latter clearly linked to the incidence of cardiovascular disease, appear increased, and levels of high-density lipoprotein (HDL), the "protective" lipoprotein, vary, depending on the hormonal concentration of the particular birth control pill. Substantial evidence exists that estrogens increase the HDL levels and progestins depress them.

Finally, only a small body of literature describes vascular wall changes in patients receiving hormonal agents. Danforth and colleagues described changes of vascular smooth muscle hyperplasia, fragmentation of the reticulum network and attenuation of the elastic tissue in rabbits administered norethynodrel and mestranol.[44] Irey and co-workers documented intimal endothelial proliferation, subendothelial fibrosis and luminal narrowing, with or without occluding thrombus, in a small number of women (20%) who died of thromboembolic disease while using an oral contraceptive[45]; these findings were not observed in a control population of women not using oral birth control medications but with fatal thromboembolic disease. They postulated there was primary endothelial damage with subsequent vascular changes and occlusion with thrombus. In the series presented here, perivascular fibrosis was seen in two patients with gangrenous small bowel.[16]

TABLE 2.—*Proposed Mechanisms of Ischemia/Infarction*

Increased	*Decreased*
Platelet aggregation	Antithrombin III level
Factor VII level and activity	Plasminogen activator level
Triglyceride level	HDL (progestins)
VLDL, LDL	

HDL = high-density lipoprotein, LDL = low-density lipoprotein, VLDL = very-low-density lipoprotein

Therefore, despite the extensive number of articles recording possible mechanisms, precisely how oral contraceptives induce an array of ischemic and necrotic intestinal changes has not been defined. The most likely explanation is a multifactorial set of conditions (increased clotting factors, altered platelet aggregation and adhesiveness, diminished fibrinolysis, elevated circulating lipoproteins and possibly primary vascular endothelial damage) that favors vascular narrowing or occlusion.

Conclusion

There appears to be a finite, although poorly quantitated, risk of vascular occlusive disease in women using oral contraceptives. Reversible small or large bowel ischemia and frank intestinal necrosis represent the two subtypes that have been described. The latter disorder carries a high mortality rate (31%). The pathophysiology is unclear and is likely complex and multifactorial. Fortunately, discontinuing oral contraceptive use seems to virtually eliminate the risk. Although the incidence of these intra-abdominal vascular complications, based on their reporting in the medical literature, seems to be decreasing concomitant with the lowering of estrogen dose, sporadic cases continue to occur. A clinician must therefore be attentive to early abdominal symptoms in women taking oral contraceptives and prescribe those preparations with the lowest hormone dosages consistent with birth control, but without breakthrough bleeding.

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